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(21) International Application Number: PCT/US97/00325 (22) International Filing Date: 7 January 1997 (07.01.97) (30) Priority Date: 08/585,005 8 January 1996 (08.01.96) US 08/667,197 20 June 1996 (20.06.96) US (71) Applicant: GENENTECH, INC. [US/US]; 460 Point San Bruno Boulevard, South San Francisco, CA 94080-4990 (US). (72) Inventors: BENNETT, Brian; 1332 Oddstat Boulevard, Pacifica, CA 94044 (US). CARTER, Paul, J.; 2074 18th Avenue, San Francisco, CA 94116 (US). CHIANG, Nancy, Y.; 622 Quintara Street, San Francisco, CA 94116 (US). KIM, Kyung, Jin; 622 Benvenue Avenue, Los Altos, CA 94024 (US). MATTHEWS, William; 560 Summit Springs Road, Woodside, CA 94062 (US). RODRIGUES, Maria, L.; 2320 Donegal Avenue, South San Francisco, CA 94080 (US). (74) Agents: HASAK, Janet, E. et al.; Genentech, Inc., 460 Point San Bruno Boulevard, South San Francisco, CA 94080-4990 (US).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(54) Title: WSX RECEPTOR AND LIGANDS (57) Abstract The WSX receptor and antibodies which bind thereto (including agonist and neutralizing antibodies) are disclosed, including various uses therefor. Uses for WSX ligands (e.g., anti-WSX receptor agonist antibodies or OB protein) in hematopoiesis are also disclosed.		

WHAT IS CLAIMED IS:

1. Isolated WSX receptor.
2. The WSX receptor of claim 1 comprising an amino acid sequence selected from the group consisting of: (a) the amino acid sequence of mature human WSX receptor variant 6.4 shown in Figs 2A-B; (b) 5 the amino acid sequence of mature human WSX receptor variant 12.1 shown in Figs. 2A-B; and (c) the amino acid sequence of mature human WSX receptor variant 13.2 shown in Figs 2A-B.
3. The WSX receptor of claim 2 which is mature human WSX receptor variant 13.2.
4. The WSX receptor of claim 1 which is WSX receptor extracellular domain (ECD).
5. The WSX receptor ECD of claim 4 which is conjugated with, or fused to, a molecule which 10 increases the serum half-life thereof.
6. The WSX receptor ECD of claim 5 which is conjugated with polyethylene glycol (PEG).
7. A composition comprising the WSX receptor ECD of claim 4 and a physiologically acceptable carrier.
8. The composition of claim 7 further comprising WSX ligand.
- 15 9. The WSX receptor of claim 1 which is chimeric WSX receptor.
10. The chimeric WSX receptor of claim 9 comprising a WSX receptor amino acid sequence fused to an immunoglobulin sequence.
11. The chimeric WSX receptor of claim 10 comprising a fusion of a WSX receptor extracellular domain sequence to an immunoglobulin constant domain sequence.
- 20 12. The chimeric WSX receptor of claim 11 wherein said constant domain sequence is that of an immunoglobulin heavy chain.
13. A method for identifying a molecule which binds to the WSX receptor comprising exposing the WSX receptor to a molecule suspected of binding thereto and determining binding of the molecule to the WSX receptor.
- 25 14. A method for identifying a molecule which activates the WSX receptor comprising exposing the WSX receptor to a molecule suspected of being capable of activating the WSX receptor and measuring activation of the WSX receptor.
15. A method for purifying a molecule which binds to the WSX receptor comprising adsorbing the molecule to WSX receptor immobilized on a solid phase and recovering the molecule from the immobilized 30 WSX receptor.
16. An antibody that specifically binds to the WSX receptor of claim 1.
17. The antibody of claim 16 which is an agonist antibody.
18. The antibody of claim 17 which has an IC50 in a KIRA ELISA of about 0.5 µg/ml or less.
19. The antibody of claim 16 which is a neutralizing antibody.

20. The antibody of claim 16 which is a human or humanized antibody.
21. The antibody of claim 16 which is an antibody fragment.
22. The antibody fragment of claim 21 which is an F(ab')₂.
23. A composition comprising the antibody of claim 16 and a physiologically acceptable carrier.
- 5 24. The composition of claim 23 further comprising a cytokine.
25. A method for activating the WSX receptor comprising exposing the WSX receptor to an amount of the antibody of claim 17 which is effective for activating the WSX receptor.
26. A method for enhancing proliferation or differentiation of a cell comprising the WSX receptor comprising exposing the cell to an amount of the antibody of claim 17 which is effective for enhancing proliferation or differentiation of the cell.
- 10 27. The method of claim 26 wherein the cell is a CD34+ cell.
28. A method for determining the presence of a WSX receptor comprising exposing a test sample suspected of containing the WSX receptor to the antibody of claim 16 and determining binding of said antibody to the test sample.
- 15 29. An isolated nucleic acid molecule encoding the WSX receptor of claim 1.
30. An isolated nucleic acid molecule encoding the WSX receptor ECD of claim 4.
31. An isolated nucleic acid molecule encoding the chimeric WSX receptor of claim 9.
32. The isolated nucleic acid molecule of any one of claims 29-31 further comprising a promoter operably linked to the nucleic acid molecule.
- 20 33. An expression vector comprising the nucleic acid molecule of any one of claims 29-31 operably linked to control sequences recognized by a host cell transformed with the vector.
34. A host cell comprising the vector of claim 33.
35. A process of using a nucleic acid molecule encoding the WSX receptor to effect production of the WSX receptor comprising culturing the host cell of claim 34.
- 25 36. A method for enhancing proliferation or differentiation of a cell comprising the WSX receptor comprising exposing the cell to an amount of WSX ligand which is effective for enhancing proliferation or differentiation of the cell.
37. The method of claim 36 wherein the WSX receptor is the WSX receptor variant 13.2.
38. The method of claim 36 wherein the cell is a hematopoietic progenitor cell.
- 30 39. The method of claim 36 wherein the WSX ligand is OB protein.
40. The method of claim 36 wherein the WSX ligand is an anti-WSX receptor agonist antibody.
41. The method of claim 36 which enhances proliferation or differentiation of lymphoid blood cell lineages.
42. The method of claim 36 which enhances proliferation or differentiation of myeloid blood cell lineages.
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43. The method of claim 36 which enhances proliferation or differentiation of erythroid blood cell lineages.
44. The method of claim 36 further comprising exposing the cell to a further cytokine.
45. The method of claim 44 wherein the further cytokine is a lineage-specific cytokine.
- 5 46. The method of claim 36 wherein the cell is present in a mammal.
47. The method of claim 46 wherein the mammal is a human.
48. The method of claim 46 wherein the mammal is suffering from, or is expected to suffer from, decreased blood cell levels.
49. The method of claim 48 wherein the decreased blood cell levels are caused by chemotherapy, radiation therapy, or bone marrow transplantation therapy.
- 10 50. A method for repopulating blood cells in a mammal comprising administering to the mammal a therapeutically effective amount of a WSX ligand.
51. The method of claim 50 wherein the blood cells are erythroid cells.
52. The method of claim 50 wherein the blood cells are myeloid cells.
- 15 53. The method of claim 50 wherein the blood cells are lymphoid cells.
54. The method of claim 50 comprising administering a further cytokine to the mammal in an amount which leads to a synergistic repopulation of the blood cells in the mammal.
55. A pharmaceutical composition comprising WSX ligand, a further cytokine, and a physiologically acceptable carrier.
- 20 56. An article of manufacture, comprising:
a container;
a label on the container; and
a composition comprising an active agent contained within the container; wherein the composition is effective for repopulating blood cells in a mammal, the label on the container indicates that the composition can be used for repopulating blood cells in a mammal and the active agent in the composition is a WSX ligand.
- 25 57. The article of manufacture of claim 56 comprising a further container which holds a further cytokine.
58. An article of manufacture, comprising:
a container;
30 a label on the container; and
a composition comprising an active agent contained within the container; wherein the composition is effective for decreasing body weight or fat-depot weight or decreasing food intake in an obese mammal, the label on the container indicates that the composition can be used for treating obesity in a mammal and the active agent in the composition is an agonist anti-WSX receptor antibody.